UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,887	09/20/2002	Yasunori Chiba	081356-0168	2894

22428 7590 02/08/2006

FOLEY AND LARDNER LLP
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
PAK, YONG D	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,887	CHIBA ET AL.	
	Examiner	Art Unit	
	Yong D. Pak	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *88-105* is/are pending in the application.

4a) Of the above claim(s) *89-91 and 95-105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88 and 92-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a 371 of PCT/JP00/05474.

The amendment filed on November 18, 2005, amending claims 88-99 and 101 , has been entered.

Claims 88-105 are pending. Claims 89-91 and 95-105 are withdrawn. Claims 88 and 92-94 are under consideration.

Election/Restrictions

Applicant's argue that Chiba et al. does not disclose the present invention. Examiner respectfully disagrees. The invention of claim 1 comprising a method f prepargin a yeast mutant comprising the disruption in its α-1,3-mannosyltransferase (MNN1) gene, mannosylphosphate transferase (MNN4) gene and α-1,6-mannosyltransferase (OCH1) gene, wherein said yeast is used in a method of producing glycoproteins is the common technical feature linking all claims. Chiba et al. discloses such a mutant yeast and a method of making the same. Chiba et al. discloses a "Strategy for genetic manipulation of S. cerevisiae" (description for Figure 1). The definition for "strategy" is "careful plan or method". In Figure 1, Chiba et al. clearly shows a method for making a "genetically manipulated S. cerevisiae" by disrupting *Δ mnn1Δ mnn4 Δ och1* and introducing α-mannosidase I and (N-acetylglucosaminyl transferase (GnT-I) genes, which are normally found in mammals and not in yeast, into said yeast to produce the yeast-hybrid complex glycoprotein. Therefore, the technical feature linking the above claims does not constitute a special

technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

Also, claims 89-91 and 95-105 are further drawn to yeast transformed with polynucleotides encoding proteins having different structure and function, which lacks the common technical feature with the method claimed in claims 88 and 92-94 and further requiring different searches in the patent and non-patent literature. Therefore, claims 88-105 do not all share a special technical feature.

The requirement is still deemed proper and is therefore made FINAL.

Claims 89-91 and 95-105 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 7, 2005.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on December 12, 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

Claim 88 is objected to because of the following informalities: the claims recite the phrase "yeast mutant". It appears that applicants have meant to recite "mutant yeast". Appropriate correction is required.

Applicants have not amended the claim nor provided any arguments. Hence the objection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88 and 92-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 88 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an α-mannosidase I and a polynucleotide encoding a GnT-I. Claims 92-93 limit claim 88 to specific auxotrophic mutations. Claim 94 is drawn to a method of preparing a mutant) yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an *Aspergillus saitoi* α-mannosidase I and a polynucleotide encoding a GnT-I. These claims are drawn to a method of (A) mutagenizing any yeast to disrupt MNN1, MNN4 and OCH1 genes by any methods and (B) transforming said mutated yeast with a polynucleotide encoding any α-mannosidase I, including any

recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including any recombinants, variants and mutants. Therefore, the claims are drawn to a method of mutagenizing any yeast that by disrupting a genus of MNN1, MNN4 and OCH1 genes and transforming said yeast with a polynucleotide encoding a genus of any α-mannosidase having any structure and a genus of GnT-I having any structure. There is insufficient descriptive support for using the above genus with respect to the yeast as well as α-mannosidase and GnT-I. The specification only teaches a method of preparing a *Saccharomyces cerevisiae* mutant by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and transforming the resulting *S. cerevisiae* mutant with a polynucleotide encoding α-mannosidase I isolated from *A. saitoi* and a polynucleotide encoding a rat GnT-I (cloned by Yoshida et al – form PTO-1449). This one example is not enough and does not constitute a representative number of all the species to describe a method of mutagenizing any or all yeast using any method and transforming the resulting yeast with a polynucleotide encoding any or all α-mannosidase I and GnT-I, including any or all mutants, variants and recombinants. Further, there is no evidence on the record of the relationship between the structure of any or all yeast and the structure of a polynucleotide encoding an *A. saitoi* α-mannosidase I and the structure of any or all recombinants, variants and mutants of a polynucleotide encoding any α-mannosidase I or the structure of a polynucleotide encoding a rat GnT-I and the structure of a polynucleotide encoding any or all recombinants, variant or mutants of any GnT-I. Therefore, the specification fails to describe a representative species of mutagenizing a

genus of yeast by disrupting a genus of MNN1, MNN4 and OCH1 genes by any methods and transforming the resulting yeast with a polynucleotide encoding a genus of α-mannosidase I and a genus of GnT-I.

Given this lack of description of the representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the inventions of claims 88 and 92-94.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov <http://www.uspto.gov>.

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the instant claims are fully described because the MNN1, MNN4 and OCH1 genes have common function and are present across multiple species of yeast in general and gives examples of three yeasts having said genes. Examiner respectfully disagrees. The claims are not limited to these three species only, but to any or all yeasts wherein said genes, including any or all recombinants, mutants or variants thereof, are disrupted by any means. Disclosure of solely functional features present in the genus is insufficient to fully describe the whole genus. As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or

chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only a few species within the genus. In the instant case the claimed genera of the claims includes species which are widely variant in structure. The claims are drawn to structurally diverse species as it encompasses any or all yeasts wherein any MNN1, MNN4 and OCH1 genes including any or all recombinants, mutants or variants thereof, normally present is said yeast or ones introduced into said yeast, are disrupted by any means. As such, the description of solely functional features present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus.

Applicants also argue that the claims are fully described because yeasts used in the present invention incorporates yeasts wherein the MNN1, MNN4 and OCH1 genes are initially present but are disrupted spontaneously and are not disrupted by any

means. Examiner respectfully disagrees. The claims do not recite the limitation that MNN1, MNN4 and OCH1 genes are initially present in the yeast. The claims, specifically claims 92 and 94, are silent of the method used in disrupting said genes. Therefore, the claims are drawn to a method of preparing a yeast by disrupting MNN1, MNN4 and OCH1 genes, either normally present in said yeast or those introduced into said yeast, by using any methods.

Applicants also argue that the claims are fully described because *S. cerevisiae* is only a representative example of yeasts and when taken into account the common technical knowledge at the time of filing of the present application, one of skill in the art would understand that the present invention can be used in other yeasts. Examiner respectfully disagrees. As discussed above, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure. A description of *Saccharomyces cerevisiae* wherein MNN1, MNN4 and OCH1 genes normally present in said yeast are disrupted with selection markers recited in claim 92 is not enough to describe a genus comprising any or all yeast wherein MNN1, MNN4 and OCH1 genes normally present in said yeast or recombinant forms of said genes, including any or all mutants or variants thereof, wherein said genes are disrupted by any methods. When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus, which applicants have failed to do.

Applicants also argue that the claims are fully described because disrupting MNN1, MNN4 and OCH1 genes with URA3 is only a representative example and that it is common technical knowledge that any auxotrophic markers can be used for disrupting genes. Examiner respectfully disagrees. The claims 88 and 94 do not recite the limitation that the MNN1, MNN4 and OCH1 genes are disrupted with said auxotrophic marker, but merely that MNN1, MNN4 and OCH1 genes are disrupted, which encompasses any methods.

Applicants also argue that the claims are fully described because any kinds of α-mannosidase I and any GnT I genes can be used in the present invention and these two genes are only representatives of genes that can be used in the present invention. Examiner respectfully disagrees. The claims are drawn to a method of using a genus of any α-mannosidase having any structure and a genus of GnT-I having any structure, including any or all recombinants, variants or mutants. As discussed above, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure. A description of transforming *Saccharomyces cerevisiae* with polynucleotide encoding α-mannosidase I isolated from *A. saitoi* and a polynucleotide encoding a rat GnT-I is not enough to describe a genus comprising any or all α-mannosidase and genus comprising any or all GnT-I, including any or all mutants or variants thereof. When there is substantial variation within the genus, one must describe a sufficient

variety of species to reflect the variation within the genus, which applicants have failed to do.

Hence the rejection is maintained.

Claims 88 and 92-94 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of preparing a mutant *Saccharomyces cerevisiae* by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and transforming the resulting mutant *S. cerevisiae* with a polynucleotide isolated from *Aspergillus saitoi* and encoding an α-mannosidase I and a polynucleotide isolated from rat and encoding a rat GnT-I, does not reasonably provide enablement for a method of preparing any mutant yeast that produces the glycoprotein of formula (IV) by disrupting any or all MNN1, MNN4 and OCH1 genes and transforming the resulting mutant yeast with a polynucleotide encoding any α-mannosidase I from any source, including recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including recombinants, variants and mutants. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4)

the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claim 88 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an α-mannosidase I and a polynucleotide encoding a GnT-I. Claims 92-93 limit claim 88 to specific auxotrophic mutations. Claim 94 is drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting MNN1 gene, MNN4 gene and OCH1 gene normally present in a wild-type yeast and transforming the resulting yeast with a polynucleotide encoding an *Aspergillus saitoi* α-mannosidase I and a polynucleotide encoding a GnT-I. These claims are drawn to a method of (A) mutagenizing any yeast, (B) disrupting MNN1, MNN4 and OCH1 genes by any methods and (C) transforming said mutant yeast with a polynucleotide encoding any α-mannosidase I, including any recombinants, variants and mutants, and a polynucleotide encoding any GnT-I, including any recombinants, variants and mutants. Therefore, the claims are drawn to a method of mutagenizing any yeast by disrupting MNN1, MNN4 and OCH1 genes having any structure in any yeast using any methods and transforming said yeast with a polynucleotide encoding any α-mannosidase having any structure I and any GnT-I having any structure.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of yeasts wherein any MNN1,

MNN4 and OCH1 genes are disrupted using any methods and wherein the resulting yeast is transformed with polynucleotides encoding any or all variants, mutants and recombinants of any α-mannosidase I and any GnT-I broadly encompassed in the method of the claims. Since applicants have not shown that the claimed method applies to all or any yeast and since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance and predictability of which specific yeast is ideal for the claimed method and which specific α-mannosidase and GnT-I is ideal to transform said mutated yeast and which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function.

However, in this case the disclosure is limited to a method of preparing a Saccharomyces cerevisiae mutant by disrupting MNN1, MNN4 and OCH1 genes normally present in *S. cerevisiae* with selection markers recited in claim 92 and transforming the resulting S. cerevisiae mutant with a specific polynucleotide isolated from A*spergillus saitoi* encoding α-mannosidase I and a polynucleotide isolated from rat encoding GnT-I (cloned by Yoshida et al – form PTO-1449), but provides no guidance with regard to a method of comprising the use of any yeast for disrupting any or all MNN1, MNN4 and OCH1 genes using any methods and transforming the resulting mutant yeast with a polynucleotide encoding any α-mannosidase I and a polynucleotide encoding any GnT-I. It would require undue experimentation of the skilled artisan to

make and use the agents in the claimed method. In view of the great breadth of the claim, amount of experimentation required to mutagenize any yeast, identify and make the polynucleotides encoding any α-mannosidase I and GnT-I, amount of experimentation required to disrupt any MNN1, MNN4 and OCH1 genes using any methods, the lack of guidance, working examples, and/or unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides and yeasts encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques and other related techniques are known, and it is routine in the art to screen for multiple strains, multiple substitutions or multiple modifications in a polypeptide as encompassed by the instant claims, the specific yeast strains required for the method and the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility for transforming said mutant yeast are limited in any protein and the result of such modifications is unpredictable. In addition, with respect to the polynucleotides encoding mannosidase and GnT-I used for transforming mutant yeast, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass a method of preparing any yeast by disrupting any or all MNN1, MNN4 and

OCH1 genes using any methods and transforming the resulting mutant yeast with a polynucleotide encoding any α-mannosidase I and a polynucleotide encoding any GnT-I because the specification does not establish: (A) said method will be successful in any or all yeasts; (B) a universal method disrupt any MNN1, MNN4 and OCH1 genes in any yeast; (C) a rational and predictable scheme for selecting agents, techniques or methods with an expectation of disrupting any MNN1, MNN4 and OCH1 genes in any yeast; (D) the general tolerance of α-mannosidase I and GnT-I to modification and extent of such tolerance; (E) a rational and predictable scheme for selecting any yeast for disrupting MNN1, MNN4 and OCH1 genes and transforming the resulting yeast with a polynucleotide encoding any α-mannosidase I and GnT-I with an expectation of making a mutant yeast that produces the glycoprotein of formula (IV); and (F) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of preparing any mutant yeast by disrupting any or all MNN1, MNN4 and OCH1 genes using any methods and transforming the resulting mutant yeast with a polynucleotide encoding any α-mannosidase I and a polynucleotide encoding any GnT. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of yeasts suitable for the above method and polynucleotides encoding an α-mannosidase I and GnT- having the

desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the instant claims are fully enabled because the MNN1, MNN4 and OCH1 genes have common function and are present across multiple species of yeast in general and gives examples of three yeasts having said genes, to show that the claims are enabled. Examiner respectfully disagrees. The claims are not limited to these three species only, but to any or all yeasts wherein said genes, including any or all recombinants, mutants or variants thereof, are disrupted by any means. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of any or all yeast wherein any or all MNN1, MNN4 and OCH1 genes, including any or all recombinants, mutants or variants thereof, are disrupted. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance and predictability of which specific yeast is ideal for the claimed method and which specific α-mannosidase and GnT-I is ideal to transform said mutated yeast and which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the

art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Applicants argue that the instant claims are fully enabled because yeasts used in the present invention incorporates yeasts wherein the MNN1, MNN4 and OCH1 genes are initially present but are disrupted spontaneously and are not disrupted by any means. Examiner respectfully disagrees. The claims do not recite the limitation that MNN1, MNN4 and OCH1 genes are initially present in the yeast. Also, claims, specifically claims 92 and 94, are silent of the method used in disrupting said genes. Therefore, the claims are drawn to a method of preparing a yeast by disrupting MNN1, MNN4 and OCH1 genes, either normally present in said yeast or those introduced into said yeast, by using any methods.

Applicants argue that the instant claims are fully enabled because *S. cerevisiae* is only a representative example of yeasts and when taken into account the common technical knowledge at the time of filing of the present application, one of skill in the art would understand that the present invention can be used in other yeasts. Examiner respectfully disagrees. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of yeasts wherein any MNN1, MNN4 and OCH1 genes are disrupted using any methods and wherein the resulting yeast is transformed with polynucleotides encoding any or all variants, mutants and recombinants of any α-mannosidase I and any GnT-I broadly encompassed in the method of the claims. Since applicants have not shown that the claimed method applies to all or any yeast and since the amino acid sequence of a

protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance and predictability of which specific yeast is ideal for the claimed method and which specific α-mannosidase and GnT-I is ideal to transform said mutated yeast and which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Applicants argue that the instant claims are fully enabled because disrupting MNN1, MNN4 and OCH1 genes with URA3 is only a representative example and that it is common technical knowledge that any auxotrophic markers can be used for disrupting genes. Examiner respectfully disagrees. The claims 88 and 94 do not recite the limitation that the MNN1, MNN4 and OCH1 genes are disrupted with said auxotrophic marker, but merely that MNN1, MNN4 and OCH1 genes are disrupted, which encompasses any methods.

Applicants argue that the instant claims are fully enabled because any kinds of α-mannosidase I and any GnT I genes can be used in the present invention and these two genes are only representatives of genes that can be used in the present invention. Examiner respectfully disagrees. The claims are drawn to a method of using any α-

mannosidase having any structure and any GnT-I having any structure, including any or all recombinants, variants or mutants. It would require undue experimentation of the skilled artisan to make and use the claimed variants and mutants of any or all α-mannosidase having and any or all GnT-I, including any or all recombinants, variants or mutants thereof. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance and predictability of which specific yeast is ideal for the claimed method and which specific α-mannosidase and GnT-I is ideal to transform said mutated yeast and which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation.

Hence the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 88 and 92-94 rejected under 35 U.S.C. 102(b) as being anticipated by Chiba et al.

Claims 88 and 92-94 are drawn to a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by disrupting a MNN1, MNN4 and OCH1 genes using the selection markers recited in claim 92 and introducing a polynucleotide encoding α-mannosidase I, such as that of *A. saitoi*, and a polynucleotide encoding GnT-I into the resulting mutant yeast.

Chiba et al. (form PTO-1449) discloses a method of preparing a mutant yeast that produces the glycoprotein of formula (IV) by transforming a *S. cerevisiae* comprising *Δ mnn1Δ mnn4 Δ och1* triple mutant with a polynucleotide encoding an *A. saitoi* α-mannosidase I and a polynucleotide encoding GnT-I into (Figure 1 and pages 26299-26300). The *S. cerevisiae Δ mnn1Δ mnn4 Δ och1* mutant was prepared by disrupting the MNN1, MNN4 and OCH1 genes with selection markers as recited in claim 92. Therefore, the reference of Chiba et al. anticipates claims 88 and 92-94.

In response to the previous Office Action, applicants have traversed the above rejection.

Applicants argue that the rejection is improper because the present invention represents for the first time a glycoprotein having a hybrid-type sugar chain represented by formula (IV) has been successfully produced in *vivo*. Examiner respectfully disagrees. This is because the claims of the instant invention are not drawn to a glycoprotein having a hybrid-type sugar chain represented by formula (IV), but to a method for preparing a yeast mutant, which Chiba et al. teaches.

Applicants argue that the present invention is not anticipated by Chiba et al. because introduction of the GnT-I gene into the mutant yeast wherein MNN1, MNN4 and OCH1 genes are disrupted have not be carried out in the laboratory. Examiner respectfully disagrees. Although Chiba et al. has not actually introduced a GnT-I gene into the mutant S. cerevisiae in laboratory settings, Chiba et al. discloses a "Strategy for genetic manipulation of S. cerevisiae" (description for Figure 1). The definition for "strategy" is "careful plan or method". In Figure 1, Chiba et al. clearly shows a method for making a "genetically manipulated S. cerevisiae" by disrupting *Δ mnn1Δ mnn4 Δ och1* and introducing α-mannosidase I and GnT-I genes, which are normally found in mammals and not in yeast, into said yeast to produce the yeast-hybrid complex glycoprotein. MPEP 2131 states "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." In the instant application, Figure 1 of Chiba et al. discloses each and every element set forth in the claims, as discussed above. Further, the claims are not drawn to a mutant yeast transformed with GnT-I, but the claims are drawn to a method of making said mutant yeast, which is clearly taught by Chiba. Also, Figure 1 outlining the method of Chiba et al. is enabling because Chiba et al. teaches yeast wherein *Δ mnn1Δ mnn4 Δ och1* are disrupted and successful expression of both α-mannosidase I and GnT-I in yeast (Pages 26300 and page 26303, last paragraph). Therefore, the reference of Chiba et al. anticipates the instant claims.

Hence the rejection is maintained.

None of the claims are allowable.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652

Manjunath Rao
Primary Patent Examiner 1652